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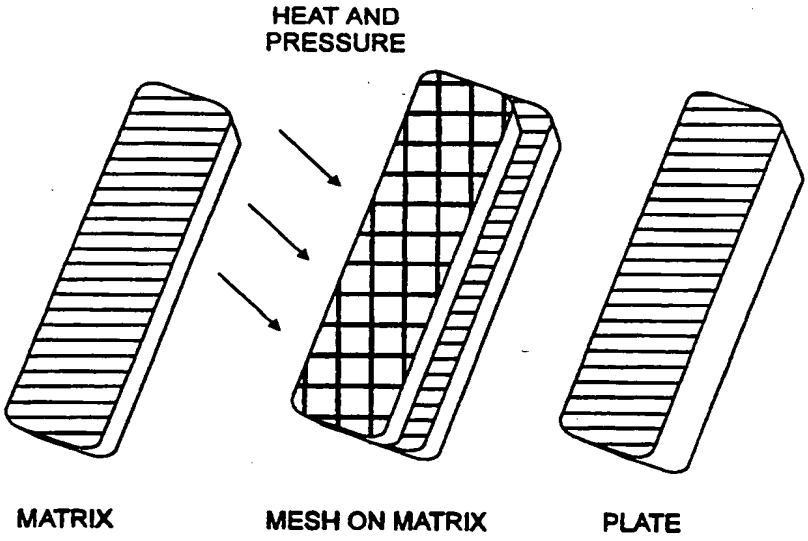

(57) Abstract

The present invention provides materials for use in biodegradable structural prosthetic devices with enhanced load-bearing strength and reinforced flexibility. Prosthetic devices are also provided, which comprise a biodegradable polymer layer, reinforced by a biodegradable material, and optionally, the inclusion of pharmacologically active substances, such as growth factors and anti-microbial agents. The prosthetic devices provide for gradually decreasing structural support that lessens as the implant degrades and is compensated by new bone growth. The degradation also provides for the controlled release of the pharmacologically active agents. The prosthetic devices are exemplified by bone fixation plates.

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DESCRIPTION

BIODEGRADABLE FRACTURE FIXATION PLATES AND USES THEREOF

BACKGROUND OF THE INVENTION

Field of the Invention

The field of the present invention relates to prosthetic devices, such as bone fixation plates, and particularly, to bone fixation plates that are biodegradable and reinforced with fibers and the like so as to provide enhance load bearing strength. The present devices and plates are also preferably fabricated so as to include growth factors, drugs and other molecules that enhance bone cell growth or have antimicrobial actions.

Related Art

Every year thousands of individuals require artificial structural bone implants, for example, facial fixation plates, long bone fixation plates, prostheses and the like. Rigid internal fixation with metallic plates and screws has become common practice in maxillofacial bone surgery. This type of fixation provides for a decreased need for immobilization of the jaws after surgery, increased ability to anatomically reconstruct the maxillofacial skeleton, and greater long term stability of the early treatment results (Terry and White, 1991; Van Sickels and Falnary, 1985). These features apply to repair of traumatic defects and fractures, reconstruction of congenital deformities and reconstruction of maxillofacial defects after tumor extirpation. However, in some cases metallic bone plates have to be removed because they are palpable or cause concerns of cosmesis. This additional surgery can cause

significant morbidity to the patient in forms of additional pain, scarring and anesthetic risk.

In the case of large bone plates for fracture repair or defect reconstruction, plates are generally removed to avoid the possibility of stress shielding (Kennedy *et al.*, 1989a; Kennedy *et al.*, 1989b). Stress shielding by metallic plates can lead to the weakening and partial resorption of the underlying bone (Paavolainen *et al.*, 1978; Simon *et al.*, 1978; Katz *et al.*, 1984). The phenomenon of stress shielding and bone remodeling was first postulated by J. Wolff in the 1970's and is known as Wolff's Law. In addition, metallic devices in the body can cause artifacts in magnetic resonance imaging and may also pose a problem for patients who have to be irradiated (Castillo *et al.*, 1988; Scher *et al.*, 1988).

The same problems outlined above also apply to the field of orthopaedic surgery. According to a recent study almost 365,000 patients in the U.S. require surgery for fracture reduction with internal fixation per year (Lemrow *et al.*). A large percentage of these patients require a second surgery for the removal of metallic fixation devices after bone healing has taken place. Many of these procedures are done in older patients who as a group do not tolerate surgery well. Also, in the treatment of children, metallic fixation devices have to be routinely removed to ensure unrestricted growth. The second surgical procedure not only adds to the discomfort and time for recuperation but also contributes to an increase in the cost of health care.

In recent years there has been tremendous interest in the development of biodegradable/bioabsorbable polymeric materials for orthopaedic applications as well as for rigid fixation of the maxillofacial skeleton (Cutright *et al.*, 1971; Cutright and Hunsuck, 1972; Bos

et al., 1987; Wittenberg *et al.*, 1991). As they biodegrade, devices made of these polymers can act as an internal fracture fixation device and promote the healthy remodeling of new bone.

In an earlier study polylactic acid (PLA) plates and screws were used for repair of unstable zygomatic fractures in a series of ten patients (Shetty and Bertolauri, 1991). However, because of the low stiffness of pure PLA material as compared to bone, this material was thought to be unacceptable for use in a high stress area, such as in the mandible. Maximum bite forces generally range from 250-1250 N, although forces in excess of 4000 N have been measured (Rugh and Smith, 1988).

Earlier, researchers have succeeded in achieving an increase in the mechanical properties of PLA by the addition of carbon fibers (Zimmermann *et al.*, 1987). However, as carbon is non-biodegradable it can potentially migrate and cause adverse tissue reactions after the PLA matrix has been fully degraded (Kelley *et al.*, 1987).

Casper (Casper *et al.*, 1984; Casper *et al.*, 1985) and Kelly (Kelley *et al.*, 1987) have reported on the use of inorganic fibers as reinforcement in a polymer matrix. Kelly *et al.* (Kelley *et al.*, 1987) tested a biodegradable composite made of calcium phosphate fibers in a matrix of PLA. The initial mechanical properties of this composite were superior compared to the polymer matrix. However, on environmental exposure in saline the strength of the composite decreased by approximately 75 percent in two weeks, possibly due to decohesion between the fibers and matrix.

Researchers have also sintered together longitudinal bundles of fibers made of polyglycolic acid (PGA) to fabricate pins or nails (Bostman *et al.*, 1989). Although these devices are fully biodegradable, their mechanical properties are enhanced predominantly in the axial direction at the expense of transverse and torsional properties. In the case of bone plates, which routinely undergo a combination of tensile, bending, and torsional loads, it is desirable to have increased strength and stiffness in all directions. In an effort to address this problem Christel *et al.* (Christel *et al.*, 1982) tested composites made with a PGA fabric in a PLA matrix. These composites did not propose the inclusion of biologically active substance such as growth factors or drugs

The elastic modulus or stiffness of bone is much higher than that of most biodegradable polymers (Daniels *et al.*, 1990). For example, cortical bone is almost five times as stiff as polylactic acid. Therefore, prosthetic devices made of biodegradable polymer alone do not have sufficient stiffness to function as prosthetic bone devices. Thus, a need remains in the medical arts for a prosthetic device that is both biodegradable and with sufficient elastic modulus (stiffness) so as to be useful in providing bone support.

SUMMARY OF THE INVENTION

The present invention seeks to overcome these and other drawbacks inherent in the prior art by providing a reinforced biodegradable prosthesis, such as a tissue plate or bone fixation plate having enhanced rigidity and support characteristics. The prosthesis is also characterized by its fabrication to include a drug or other pharmacologically active factor(s). The pharmacologically active factor or factors will generally

accelerate and/or foster tissue growth, and most particularly bone formation, and/or aid the prevention of microbial activity, e.g., as seen in nosocomial infectious disease. The controlled release of growth factors and anti-microbial agents is achieved by the slow release of these factors/agents as the prosthesis degrades.

The devices of the present invention are biodegradable. This characteristic imparts to the inventive prosthetic appliances a number of advantages. For example, a biodegradable fixation device, unlike a counterpart metal device, will not present long-term corrosion related complications. Conventional, non-biodegradable prosthetic materials are also a source for infection. Thus, a biodegradable material used as the invention will decrease the long term risk of such infection. Also, biodegradable devices will gradually transfer load to the newly formed bone as they biodegrade, thus preventing stress shielding and the consequent stress protection atrophy of the bone.

In practicing the invention, one can employ any drug used to treat the body and capable of diffusing through a polymeric membrane at a therapeutically effective rate. The term "drug" as used herein and is intended to be interpreted in its broadest sense to include any composition or substance that will produce a pharmacologic response either at the site of application or at a site remote therefrom.

Suitable drugs for use in therapy with the drug-delivery system of the invention include, without limitation:

1. Anti-infectives, such as antibiotics, including penicillin, tetracycline, chlortetracycline

bacitracin, nystatin, streptomycin, neomycin, polymyxin, gramicidin, oxytetracycline, chloramphenicol, and erythromycin; sulfonamides, including sulfacetamide, sulfamethazine, sulfadiazine, sulfamerazine, sulfamethizole and sulfisoxazole; anicomycin, antivirals, including idoxuridine; and other anti-infectives including nitrofurazone and sodium propionate;

2. Anti-allergenics such as antazoline, methapyrilene, chlorpheniramine, pyrilamine and prophenpyridamine;

3. Anti-inflammatories such as hydrocortisone, cortisone, dexamethasone 21-phosphate, fluocinolone, triamcinolone, medrysone, prednisolone, prednisolone 21-phosphate, and prednisolone acetate;

4. Estrogens such as estrone, 17β-estradiol, ethinyl estradiol, and diethyl stilbestrol;

5. Progestational agents such as progesterone, 19-norprogesterone, norethindrone, megestrol, melengestrol, chlormadinone, ethisterone, medroxyprogesterone, norethynodrel and 17α-hydroxy-progesterone;

6. Humoral agents such as the prostaglandins, for example, PGE_1, PGE_2, and PGF_2;

7. Antipyretics such as aspirin, sodium salicylate, and salicylamide;

8. Nutritional agents such as essential amino acids and essential fats.

9. Growth factors, such as bone morphogenic protein (BMPs).

Other drugs having the same or different activity as those recited above can be employed in drug-delivery systems within the scope of the present invention.

Drugs can be in different forms, such as uncharged molecules, components of molecular complexes, or non-irritating, pharmacologically acceptable salts such as hydrochloride, hydrobromide, sulphate, phosphate, nitrate, borate, acetate, maleate, tartrate, salicylate, etc. For acidic drugs, salts of metals, amines, or organic cations (e.g. quaternary ammonium) can be employed. Furthermore, simple derivatives of the drugs (such as ethers, esters, amides, etc.) which have desirable retention and release characteristics but which are easily hydrolyzed at physiological pH, enzymes, etc., can be employed.

The amount of drug incorporated in the drug-delivery device varies depending on the particular drug, the desired therapeutic effect, and the time span for which the device provides therapy. Since a variety of devices in a variety of sizes and shapes are intended to provide dosage regimes for therapy of many different maladies, there is no particular critical upper limit on the amount of drug to be incorporated in the device fabricated according to the present invention. The lower limit too will depend on the activity of the drug and the time span of its release from the device. Thus, those of skill in the art will be able to readily identify suitable ranges of drugs for use as therapeutically effective amounts in the practice of the present invention.

The present invention provides a biodegradable reinforcement material for a prosthetic device. In one

embodiment, the material comprises one or more biodegradable polymer layers and one or more biodegradable reinforcement structures dispersed within the polymer layers. The biodegradable reinforcement structure preferably comprises a multi-directional (i.e., more than one direction) arrangement of fibers, spheres or particles dispersed within the polymer layer. The load bearing strength of the material is thus increased without significantly increasing the stiffness of the polymer layer.

The fibrous biodegradable reinforcement structure may comprise any variety of materials. Most preferably, the biodegradable reinforcement structure comprises interwoven threads of PLA and/or PGA, or interwoven threads made of a mixture of PLA and PGA. Alternatively, the biodegradable reinforcement structure, biodegradable mesh is to be made of a biodegradable yet high molecular weight polymer or resin. One example of an appropriate material is Vicryl®. Vicryl® is a special combination of PLA-PGA and it is used to fabricate the mesh. Vicryl® is 90%-10% PGA-PLA.

In a most preferred aspect of the reinforcement material, the interwoven polymer threads comprise about a 100% PLA. The reinforcement structures may alternatively comprise biodegradable ceramic fibers or beads, or polymer, particularly high molecular weight polymer, beads.

Turning now to a description of still another aspect of the invention, a prosthetic device comprising at least two layers of the biodegradable reinforcement materials described herein is disclosed. These prosthetic devices, in preferred aspects, further comprise a pharmaceutically effective amount of a pharmacologically active agent embedded within or otherwise associated with the

polymeric fibers dispersed between the layers of the biodegradable reinforcement materials. By way of example, such a pharmacologically active agent is a BMP. The inclusion of one of these particular agents would be particularly desired where, for example, the prosthesis is to be used in conjunction with a bone surface, i.e., as a biodegradable bone fixation plate. Other pharmaceutically active agents, such as anti-microbial agents and/or the materials listed herein, may also be employed in conjunction with the various forms of the prosthetic device disclosed herein.

In one particularly preferred embodiment, the present invention provides a biodegradable polymeric fracture fixation plate (BFP) using polymeric fibers, such as part of an interwoven mesh of fibers, for reinforcement. It is expected that the mesh will provide reinforcement in multiple directions. Additionally, fiber-matrix decohesion will be minimized where both the fiber mesh and the matrix materials used in making the invention belong to the same family of biodegradable materials. Other family members include polylactic acid, polyglycolic acid and their copolymers.

In most preferred embodiments, the prosthetic device will comprise at least two, preferably between about 10 and about 20 layers, or about 12, about 15, or about 18 layers, of the biodegradable reinforcement films described herein. In such aspects, the biodegradable reinforcement structure dispersed within each layer comprises an interwoven fibrous mesh of PLA and PGA fibers. Alternatively, the reinforcement structure may constitute a biodegradable ceramic mesh or beads.

The present invention also provides methods of making the biodegradable prosthesis described herein. In one preferred aspect, the method comprises the steps of

casting a biodegradable polymer film, dispersing a biodegradable reinforcement structure into said polymer to form a reinforced film, stacking layers of the reinforced film, and sintering the stacked layers of the film together to form a plate, this plate providing a prosthesis structure. Most preferably, the reinforcement material to be dispersed within each biodegradable polymer film comprises interwoven fibrous PLA threads, or alternatively, interwoven fibrous PGA threads, or a mixture of PLA and PGA interwoven threads. Where threads made of a mixture of PLA and PGA are contemplated, the threads comprise about 10% PLA and about 90% PGA.

As defined above, the sintering step of the method may be further described as comprising pressurizing and heating the film layers in a hydraulic press. However, alternative techniques for sintering at least two layers of a polymer film together may be used with equal efficacy. For example, sintering of polymeric layers may be achieved by chemically melting the contacting surfaces of the films before applying pressure according to techniques well known to those of skill in the art.

To maximize the strength of the layered polymer films, the structure will most preferably constitute a series of layers stacked so as to achieve a 90 degree angle between the orientation of the reinforcement threads in each layer relative to each preceding layer in the device. For example, in one embodiment, it is contemplated that the biodegradable reinforcement structures constitute an interwoven series of polymer threads dispersed within the polymer film in a bidirectional orientation. Accordingly, each polymer film would be arranged relative to its preceding film by orienting the fibers in a direction perpendicular to the fibers in the previous layer.

Biodegradable bone-fixation devices of the present invention are particularly attractive because, unlike metals, they will not present long term corrosion related complications. Also, the biodegradable devices of the present invention gradually transfer load to the newly formed bone as they biodegrade, thus preventing stress shielding a consequent stress atrophy to bone.

The biodegradable plates of the present invention are reinforced, such as by fibers, and thus have enhanced load-bearing properties and suitability for use in fracture fixation and other prosthetic uses.

The present invention provides prosthetic devices that are capable of supporting mechanical stress, are biodegradable, and allow for the transfer of mechanical stress to the newly formed tissue, such as bone, by the incorporation of strength-promoting fibers within the polymer plate. This approach preserves maximal strength promoting characteristics to the prosthetic device without significant additional weight, and further preserves the overall flexibility of the device.

In the past, those in the art have attempted to develop biodegradable fixation plates with limited success. The present inventors supplement their basic biodegradable material invention with the incorporation of bone growth factors and/or other drugs and proteins in a biodegradable bead or fiber-reinforced plate. As the fixation devices biodegrade *in vivo*, they simultaneously release the growth factors and/or drugs incorporated therein, thereby accelerating bone repair and assisting in wound healing.

These devices will not only eliminate the problems associated with metallic devices, but will also reduce the incidence of fracture non-unions. Fully

biodegradable fracture fixation plates (BFP) reinforced with biodegradable fibers, such as a fiber mesh, have been successfully produced by the inventor. Functional models coated with protein factors are also provided in the present disclosure, and illustrate the utility of the present inventive fracture fixation plates with pharmacologically active drugs.

As used herein the terms "elastic modulus" and "stiffness" are used interchangeably. These terms are used to define the resistance to deformation exhibited by the biodegradable prosthesis, as measured by 3-point bend tests. ASTM standard D790-86.

The growth-promoting factors used with the present invention are defined as proteins or polypeptides that are osteoinductive, *viz.* factors that are capable of stimulating bone cell growth. As used herein, the term "stimulate bone cell growth" refers to the capacity of a given composition to promote the growth or proliferation of normal bone cells to any detectable degree. Accordingly, growth factors for use with the present invention are functionally characterized as having the ability to stimulate the growth of bone cells, as exemplified by an ability to stimulate the growth of osteoblasts in culture; or the ability to stimulate the in-growth of bone cells into the surface pores of a prosthesis.

Anti-microbial agents for use with the present invention are generally characterized as having substantial anti-microbial or anti-bacterial activity. As used herein the term "substantial antimicrobial or anti-bacterial activity" describes agents capable of killing or preventing the growth of microbes defined herein as organisms capable of colonizing the prosthesis and the host organism, such as bacteria and fungi.

As used herein, the terms "cast" and "casting", are used to describe the chemical formation of a biodegradable polymer film. The incorporation of a fibrous reinforcement is accomplished by stacking layers of a biodegradable mesh, such as Vicryl®, at about a 90° angle from a previous stacked layer to form said film layer. Other biodegradable reinforcement mesh may be used with the present invention, for example pure PLA or PGA mesh, as well as other commercially available biodegradable materials known to those of ordinary skill in the art. "Sintering" is used to describe a means of solidifying the present invention by the use of heat, pressure, desiccation, or any combination thereof.

A particularly important feature of the claimed device is that the prosthesis serves both as a fracture fixation device and a controlled drug release system. Another feature of the device is that it also provides for the slow release of drugs and growth factors in a controlled manner over a prolonged period of time (weeks or months), wherein the rate and duration of the drug/growth factor release can be manipulated. The prosthesis also provides support to fractured bone, alleviating the problem of stress shielding and related bone atrophy. Another important feature of the device is that it is fully biodegradable *in vivo*.

Even though the invention has been described with a certain degree of particularity, it is evident that many alternatives, modifications, and variations will be apparent to those skilled in the art in light of the foregoing disclosure. Accordingly, it is intended that all such alternatives, modifications, and variations which fall within the spirit and the scope of the invention be embraced by the defined claims.

BRIEF DESCRIPTION OF THE FIGURES

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

FIG. 1. Schematic showing fabrication technique for BFP.

FIG. 2. Functional models of BFP's shown along with metallic fixation plates.

FIG. 3. Elastic modulus vs. weight fraction of mesh for BFP. The data shows Row increasing the amount of reinforcing mesh in the BFP increases its stiffness.

FIG. 4. *In vivo* photograph of BFP supporting a transcortical fracture.

FIG. 5. Stress vs. deformation curve for dry BFP. The slope of the linear portion of the curve as an indicator of the stiffness.

FIG. 6. Stress vs. deformation curve for BFP soaked in phosphate buffered saline (PBS) for 8 weeks.

FIG. 7. Provide a MRI photo of BFP on rabbit femur after 8 weeks *in vivo* cross section of femur. The dark outline shows cortical bone; white areas indicate fluid infiltration.

FIG. 8A and FIG. 8B. Affects of mesh weight faction (FIG. 8A) failure stress and (FIG. 8B) elastic modules of BFP.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

To successfully develop biodegradable, fracture fixation devices using polymers, the present invention increased the stiffness and strength of polymers by incorporating reinforcing fibers in a polymeric fixation plate or other prosthetic device. Instead of using unidirectional fibers for reinforcement, the present invention discloses bi-directional fibers that form a reinforcing structure in the plate, particularly in the form of an interwoven mesh of fibers. Most preferably, the fibers are made of Vicryl®.

Layers of a biodegradable mesh made of Vicryl® are incorporated in a matrix of PLA using heat and pressure in the preparation of preferred embodiments of the plates of the present invention. Compared to plates fabricated from PLA with no mesh, these plates are expected to have improved properties both in the axial and transverse directions.

Materials and Methods

It has been established that both PLA and PGA are fully biocompatible and do not cause any significant adverse reactions *in vivo* (Kulkarni *et al.*, 1971). PLA has superior mechanical properties relative to other biodegradable polymers and depending on its molecular weight it can take six months or more to fully biodegrade (Miller *et al.*, 1977). Using PLA with a starting molecular weight of 85 Kda, Miller *et al.* (Miller *et al.*, 1977) determined that 70 percent of the implant remained intact after 12 weeks of implantation in a rat model, and PLA has a half-life of 6.6 months *in vivo*. These properties make PLA an ideal candidate for the matrix material in the biodegradable fixation plates of the present invention.

Specimen Preparation

Functional models of the fixation plates were successfully fabricated in the inventor's biomaterials laboratory. The first functional models developed by the inventors had a matrix of a 50%-50% copolymer of PLA and PGA, and were reinforced by a biodegradable surgical mesh made of Vicryl®. Vicryl® is composed of 90% PGA/10% PLA. To fabricate the functional models, films of the PLA-PGA copolymer were solution cast from an acetone solution. The films were then dried under conditions of controlled temperature and air flow. The average thickness of these films was approximately about 250 μm. Alternate layers of this film and the mesh were then stacked (up to a maximum of 50 total layers) in a stainless steel mold. Next the mold was pressurized and heated in a hydraulic press to sinter the layers together into a plate form of approximate size 50 x 8 x 3 mm (L x W x D) (FIG. 1). The resulting BFPs are shown in FIG. 2. The screw holes were added at a later stage. The next stage of functional model prosthesis development used 100% PLA (intrinsic viscosity = 0.7 Dl/g) as the matrix material. BFPs were fabricated using PLA films solution cast from methylene chloride. A weight-fraction (defined as the ratio of the weight of the mesh to the weight of the whole composite) of approximately 0.25 was used.

Mesh Orientation

A commercially available surgical mesh was used in this study for the reinforcing element in composite bone plates from Ethicon Inc. This mesh is available as a weave with fiber bundles aligned at 90 degrees to each other (0°, 90°). Long-fiber composite materials are anisotropic in nature and fiber orientation is an important parameter in determining the elastic modulus or stiffness of a composite. This stiffness is highest if

the load is applied parallel (longitudinal) to the axes of the fibers, and is lowest when the load is perpendicular (transverse). Because under *in vivo* conditions the loading on the BFP will be complex, and will include both axial and perpendicular components simultaneously, it is important that the BFP has fiber reinforcement in multiple directions. The fixation plates were fabricated using a stacking sequence:

$$0°,90°/0°,90°/0°,90°$$

where the specified angles are measured with respect to the longitudinal or axial direction of the composite BFP.

Bone Growth Inducing Factors

Bone morphogenetic proteins are now readily available (Wozney *et al.*, 1988; Rosen *et al.*, 1989; Alper, 1994). BMPs are members of the transforming growth factor-β (TGF-β) superfamily. Other TGF molecules have also been shown to participate in new bone formation, and TGF-β is regarded as a complex multifunctional regulator of osteoblast function (Centrella *et al.*, 1988; Carrington *et al.*, 1969-175; Seitz *et al.*, 1992). Indeed, the family of transforming growth factors (TGF-α and TGF-β) has been proposed as potentially useful in the treatment of bone disease (U.S. Patent 5,125,978, incorporated herein by reference). TGFs and BMPs each act on cells via complex, tissue-specific interactions with families of cell surface receptors (Roberts & Sporn, 1989; Paralkar *et al.*, 1991).

Recently, eight distinct BMP proteins have been identified, designated BMP-1 through BMP-8. BMPs 2-8 are generally thought to be osteogenic, whereas BMP-1 may be a more generalized morphogen (Shimell *et al.*, 1991).

BMP-3 is also called osteogenin (Luyten *et al.*, 1989) and BMP-7 is also called OP-1 (Ozkaynak *et al.*, 1990).

Osteogenic factors (U.S. Patents 4,877,864; 4,968,590; 5,108,753) and BMP proteins may be prepared as described in the patent literature, for example, in U.S. Patents 5,108,922 (BMP-1); 5,166,058 and 5,013,649 (BMP-2, BMP-2A and BMP-2B); 5,116,738 (BMP-3); 5,106,748 (BMP-5); 5,187,076 (BMP-6); and 5,108,753 and 5,141,905 (BMP-7); all incorporated herein by reference. Osteogenic proteins designated OP-1, COP-5 and COP-7 are also disclosed in U.S. Patent 5,011,691. Although the BMP terminology is widely used, it may prove to be the case that there is an OP counterpart term for every individual BMP (Alper, 1994). Any of the foregoing proteins may be used in the biodegradable prostheses and fracture plates of the present invention.

Other growth factors/hormones besides TGF and BMP may influence new bone formation following fracture. Bolander and colleagues injected recombinant acidic fibroblast growth factor into a rat fracture site (Jingushi *et al.*, 1990), resulting in a significant increase in cartilage tissue in the fracture gap at high doses. Estrogen may also have a role in normal fracture repair (Boden *et al.*, 1989).

Various other proteins and polypeptides that have been found to be expressed at high levels in osteogenic cells may also be used in the invention. For example, macrophage colony stimulating factor (Horowitz *et al.*, 1989) and Vgr-1 (Lyons *et al.* (1989). Osteotropic agents such as lipopolysaccharide, PTH1-84, PTH1-34, vitamin D and all-trans retinoic acid may also be employed.

Calcium regulating hormones such as parathyroid hormone (PTH) participate in new bone formation and bone

remodeling (Raisz & Kream, 1983). PTH is an 84 amino acid calcium-regulating hormone whose principle function is to raise the Ca^{+2} concentration in plasma and extracellular fluid. Studies with the native hormone and with synthetic peptides have demonstrated that the amino-terminus of the molecule (aa 1-34) contains the structural requirements for biological activity (Tregear *et al.*, 1973; Herrmann-Erlee *et al.*, 1976; Riond, 1993). Chronic, low dose administration of the amino-terminal fragment of PTH (aa 1-34) induces new bone formation, according to a time- and dose-dependent schedule (Selye, 1932; Parsons & Reit, 1974). PTH and active fractions thereof may thus be used in the present inventive compositions and methods.

Evidence of synergistic interactions between hPTH-1-34 and other anabolic molecules has been presented, including insulin-like growth factor, BMP-2, growth hormone, vitamin D, and TGF-β (Slovik *et al.*, 1986; Spencer *et al.*, 1989; Mitalk *et al.*, 1992; Canalis *et al.*, 1989; Linkhart & Mohan, 1989; Seitz *et al.*, 1992; Vukicevic *et al.*, 1989). Accordingly, combinations of these or other such proteins may be used in the biodegradable fracture plates and prostheses described herein.

Indeed, studies have been conducted in which preparations of protein growth factors, including BMPs, have been administered to animals in an effort to stimulate bone growth. The results of four such exemplary studies are described in Toriumi *et al.* (1991) and Yasko *et al.* (1992), concerning BMP-2; and Chen *et al.* (1991) and Beck *et al.* (1991), concerning TGF-β1. Studies such as these have thus established that exogenous growth factors can be used to stimulate new bone formation/repair/regeneration *in vivo*.

Certain U.S. Patents also concern methods for treating bone defects or inducing bone formation. For example, U.S. Patent 4,877,864 relates to the administration of a therapeutic composition of bone inductive protein to treat cartilage and/or bone defects; U.S. Patent 5,108,753 concerns the use of a device containing a pure osteogenic protein to induce endochondral bone formation and for use in periodontal, dental or craniofacial reconstructive procedures. While not being limiting in any way or intended as a replacement of the judgement of the practitioner, the doses in patents and scientific articles such as those described above are useful as guidelines for establishing effective amounts of bone growth-inducing factors for use with the biodegradable implants of the invention.

Effects of Mesh Weight Fraction

The weight fraction (wf) as defined in the present invention is the ratio of the weight of the mesh to the weight of the whole composite. Computer-based stress analysis has determined that the stiffness of the composite plate is an increasing function of the fiber weight fraction (FIG. 3). The functional models developed for the preliminary studies were fabricated using a weight fraction of approximately 0.25.

The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are

disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

EXAMPLE 1

FABRICATION OF BIODEGRADABLE FRACTURE FIXATION PLATE

A fully biodegradable fracture fixation plate (BFP) was fabricated using a biodegradable polymer reinforced with a mesh or fibers of a similar polymer. Bone growth factors and/or drugs were incorporated in the plates. Such a plate initially provides support to the bone at the fracture site and then is gradually biodegraded. As the BFP biodegrades it releases the bone growth factors included within the polymer at the injury site and accelerates bone formation. The drugs, e.g. antibiotic, fight infections and assist in wound healing.

Functional models of BFP have been successfully fabricated in the inventors biomaterials laboratory. The models developed by the inventors are reinforced by a biodegradable surgical mesh made of, for example, Vicryl®. To fabricate the models, films of the biodegradable polymer (e.g., polylactic or polyglycolic acids) were solution cast from an organic solvent (e.g., acetone, methylene chloride). The films were then dried under conditions of controlled temperature and air flow. The average thickness of these films was approximately 250 μm. Alternate layers of this film and the mesh were then stacked (up to a maximum of 50 total layers) in a mold. Next the mold was pressurized and heated in a hydraulic press to sinter the layers together into a plate form (FIG. 1).

The resulting BFPs are shown in FIG. 2. The screw holes may be added at a later stage. It is also possible to cast the films on the mesh itself to create layers of

pre-pregs. These pre-pregs can then be stacked in the mold, heated and pressurized. Functional models using this technique have also been fabricated.

To retard the rate of biodegradation, the BFP is coated with thin layers of a slower degrading polymer, e.g. polycaprolactone (PCL). For instance, PCL will be dissolved in an organic solvent and the BFP repeatedly immersed in it (for preferably less than about 5 seconds) and dried.

Growth factors and drugs are also incorporated in the biodegradable fixation plates of the invention using the technique disclosed hereinbelow. Models of the BFP have been fabricated in the following fashion using soybean trypsin inhibitor. The use of this protein demonstrates the utility of the claimed fixation plates with other bioactive proteinaceous materials, most particularly osteoconductive and osteoinductive substances. By way of example, such substances include bone morphogenic proteins (BMPs) and TGF1β.

One particular preferred method to accomplish this is by preparing a solution of a biodegradable polymer in an organic solvent, suspending a protein in the solvent and stirring to obtain an even dispersion, and immersing the biodegradable fixation plate into the dispersion. The biodegradable fixation plate may be repeatedly immersed in the dispersion until several layers of the immersion polymer dispersion is formed onto the fixation plate. The number of layers of the dispersion will dictate the dose of the drug or protein in the BFP.

EXAMPLE 2

IN VITRO EVALUATION OF BFP

Nine (9) biodegradable fixation plates were fabricated from 100% PLA and divided into three groups (A, B, and C) of 3 specimens each. Specimens from Group A did not have any screw holes. Groups B and C had 4 screw holes (diameter 4.0 mm) introduced in each specimen. Specimens from these two groups were then fastened to plates of Plexiglass® to simulate plating on bone. Group C was then subjected to degradation in phosphate buffered saline (PBS) at 37°C for a period of 8 weeks. At the end of the test period these specimens were removed and their mechanical properties analyzed. As the specimens underwent degradation in PBS at 37°C, their mechanical properties were affected. Groups A and B had a degradation period of 0 weeks and served as the controls. Because the BFPs are load carrying implants, their mechanical properties, e.g., elastic modulus, yield strength and fracture strength, are of primary interest. Therefore, these properties as well as the mass of the implant were monitored during this study.

In Vitro Evaluation

Mechanical Testing

Upon mechanical testing, specimens from Group A yielded a elastic modulus of approximately 3.1 Gpa in 3-point bend tests. The apparent elastic modulus for Groups B and C is shown in Table I. The latter two groups yielded only apparent elastic modulus because the specimens had screw holes and were not standard test specimens. Representative stress-strain plots for these groups are shown in FIG. 5 and FIG. 6. At the end of 8 weeks of degradation in PBS, Group C exhibited a decrease of approximately 77 percent in its apparent stiffness.

Magnetic Resonance Imaging

Results indicated that the T1 is shorter in the center when compared to the edge. Also, the T1 of water was longer than the edge. This indicates that hydrolysis has an effect on the relaxation time of the BFP and this effect probably occurs in a gradient across the sample as it comes in contact with water. A distinct hydration gradient across the specimen was detected in 100% PLA specimen hydrated for 4 weeks.

Mechanical Properties

The specimens were subjected to a 3-point bending test using a tensile testing machine as per ASTM (American Society for Testing of Materials) standard D790-81. The specimens were tested at room temperature in an Instron tensile testing machine using a cross-head displacement speed of 0.05 in/min (1.3 mm/min.). The following properties of the composite in bending were determined: elastic modulus, E; fracture strength, σf; and the yield strength, σy.

Magnetic Resonance Imaging (MRI)

A GE CSI/45 2T Chemical Shift Imager was used for *in vitro* MRI study. Data acquisition parameters have been establish for the proposed study based on preliminary investigations from other studies (Alder *et al.*, 1992; Potter, 1991). Initially, images were obtained with an 12 mm surface coil (18 gauge insulated copper wire, three turn) tuned to protons (^1H).

There is typically a rapid decrease in sensitivity of a surface coil at increasing distance from the coil. The sensitive volume generated by the coil does not have hard boundaries; its detailed shape is quite complex and

dependent on the parameters used in the study. The spatial variation of sensitivity throughout a sample is directly related to the spatial variation of the radio-frequency (rf) field produced by the coil. This rf inhomogeneity, characteristic of all surface coils, is in contrast to solenoidal type coils that are designed to optimize rf uniformity across the sample being evaluated. Therefore, while the original surface coil supplied spectra with good baseline separation of the resonant peaks, the need for uniformity of the field across the sample dictated a coil design of optimal homogeneity. Images were also obtained using a 16 mm solenoidal coil (18 gauge insulated copper wire, six turn) tuned to protons (^1H). This design generated the desired uniform radio-frequency field over the entire exposure volume, helping to eliminate potential sampling errors characteristic of surface coils.

In vitro imaging of the 50%-50% PLA-PGA functional prosthesis model was successfully performed using magnetic resonance. The fixation plates were hydrated for 48 hours prior to imaging. Also, in this study an attempt was made to study the extent of water infiltration in a BFP using MRI. Since PLA-PGA degrades by hydrolysis, its degree of *in vivo* biodegradation can be gauged by monitoring the amount of water in the plate.

For this study, samples of the fixation plate that had been hydrated for up to 4 weeks in normal saline were used. T1 or longitudinal relaxation was measured using the magnetic resonance instrument described above. T1 is defined as the re-establishment of a magnetization equal to M_o along the z-axis (in the longitudinal direction). The T1 relaxation rate or relaxation time in a particular tissue, or, as in this study, a sequentially hydrating BFP, depends on the properties of the tissue or material. As the fixation plate absorbs more and more water, the T1

is expected to change. Inversion recovery images were obtained from the 50%-50% PLA-PGA samples. The inversion recovery images (180-90-180) were performed in three places: 1) the center of the BFP, 2) the edge of the BFP, and 3) the water surrounding the BFP. The inversion pulse delay was varied from 26 microseconds to 950 microseconds.

Statistical Analysis

All measurements were compiled in tables as means and standard deviations. The degradation time was the only source of variance in the measured properties of the material.

TABLE I

Specimen Type	Apparent Elastic Modulus (Gpa)	Fracture Stress (Mpa)
Control (dry) BFP without holes	3.15±0.39	45.02±10.89
Control (dry) BFP with holes	2.91±0.20	44.83±02.70
BFP soaked in PBS for 8 weeks	0.66±0.05	4.87±0.79

EXAMPLE 3

***IN VIVO* EVALUATION OF BIODEGRADABLE FIXATION PLATE INCLUDING BONE MORPHOGENIC PROTEINS**

In vivo studies of the BFP in five mature, male New Zealand rabbits were used for the *in vivo* evaluation. Four of these animals underwent a surgical osteotomy ("fracture") of the femur. The osteotomy involved a complete saw cut through the femur. These femurs were then fitted with the fixation plate with bone morphogenic proteins. (FIG. 4). Titanium metal screws were used for this purpose because the use of biodegradable screws would add yet another variable to the study. Titanium was used instead of stainless steel because it does not interfere with MRI. The simulated fracture site provided

for BFP evaluation in a simplified loaded condition. One animal served as the control and was fitted with a BFP without an osteotomy of the femur. All surgical procedures were performed under general anesthesia in appropriately prepared animals. Radiographs and MRIs of the femurs were obtained in both the test group and the control.

In Vivo Magnetic Resonance Imaging

Imaging procedures was performed using the GE CSI/45 2T Chemical Shift Imager. Each data collection session consisted of proton imaging and required that the animal be chemically restrained (general anesthesia) in the instrument for 20 to 40 minutes. MRI utilized a solenoid coil to obtain T1 and proton weighted cross-sectional images. Image slices included BFP over normal bone and BFP over osteotomy site. Localized relaxation measurements will be made utilizing these images.

The rf coil was placed in a cradle that supported the subject's leg in the X-dimension of the spectrometer with the coil encompassing the leg. Magnetic field homogeneity was measured by proton line width for all proton imaging studies. All of the data was acquired using a 2.0 Tesla 45 cm bore General Electric CSI-II Imaging Spectrometer equipped with an Oxford superconducting magnet.

Results

Magnetic Resonance Imaging

MRI of the control animal four weeks post-operation showed the BFP intact. Hydrolysis of the BFP was clearly visible as shown in FIG. 7. The *in vitro* testing indicates that the 100% PLA specimens lost approximately

77% of their stiffness during 8 weeks of biodegradation. To be successful *in vivo* a BFP would be required to provide support to the bone up to 6 weeks.

The polymer used in the study had a molecular weight of approximately 70 kD and a inherent viscosity of 0.7 Dl/g. Since the stiffness of a polymer is an increasing (though weak) function of its molecular weight and viscosity, a polymer with an inherent viscosity of about 2.9 to 3.0 Dl/g, specifically about 2.9 Dl/g was used for the next iteration. Also, the weight fraction of the mesh in the BFP was increased. Additionally, incorporating BMP in the plate accelerates the healing process and the demands on the life of the BFP will decrease.

The screw holes were too large for the width of the plate and weakened the plate. The screw holes appeared to be approximately 4.5 mm in diameter and consequently the ligaments of material on either side of the holes were not sufficient to support the imposed loads. Screw holes with a 2 mm diameter are thus proposed.

Both the *in vivo* and *in vitro* studies have indicated that MRI is a viable technique to study the fluid infiltration into the BFP. It also provides a means of imaging the plates *in vivo* since they are radio-opaque.

The results of this study allow the development of fracture fixation devices that will biodegrade in the body and will not have to be surgically removed. These devices will decrease morbidity and mortality by avoiding a second surgery and concomitant anesthesia altogether and also decrease the chance of infection and its concomitant risks of sepsis. Thus, such devices will lead to a decrease in man-hours lost due to surgery, patient discomfort, and in health care costs. Bone

fixation plates that incorporate drugs (antibiotics) and growth factors are also provided. Magnetic resonance findings with the BFP will allow expand use of this non invasive imaging technology in the imaging and evaluation of implants practiced according to the present invention.

EXAMPLE 4

OPTIMIZED FABRICATION TECHNIQUES

New techniques were developed for fabrication of the BFP to optimize the quality of these plates. BFP with reinforcing mesh weight fractions (wt. of mesh ÷ wt. of plate) of 0, 0.4, 0.5 and 0.6 were fabricated using these new techniques and tested for mechanical properties. *In vitro* biodegradation studies of additional sets of 0.5 and 0.6 mesh weight fraction (wf) plates have been initiated along with magnetic resonance imaging to detect fluid infiltration. The details of the accomplishments are discussed below:

Fabrication:

The prototype BFPs fabricated and tested during the study yielded an elastic modulus (stiffness) of 3.1 Gpa in 3-point bend tests. To enhance this stiffness, the following procedures were developed:

(1) The molecular weight of the polylactic acid (PLA) used for the BFP matrix was increased to 265,000 daltons (inherent viscosity 2.9).

(2) The reinforcing knit mesh was replaced by a biodegradable woven Vicryl® mesh.

(3) The PLA films were cast on the mesh from a dilute solution in methylene chloride in a 0°C environment to prevent bubbles or cavities.

(4) These films were preheated in a vacuum at 65°C to degas the material. This procedure eliminated bubbles and holes in the plates.

(5) Films were then stacked and prepressed in the mold under 3-4 tons for 30 minutes using a Carver press to obtain uniform contact between the films and prevent decohesion.

(6) The BFPs were fabricated using a lower temperature (330°F) but higher pressure (3 tons) compared to the original procedure. The resulting plates exhibited an increase in ductility and stiffness.

Successful development of the above techniques required the fabrication and testing of approximately 50 to 60 GFPs.

Mesh Weight Fraction:

Using the fabrication protocol described above, BFPs with four different mesh weight fractions 0.0 (n=4), 0.4 (n=5), 0.5 (n=8), and 0.6 (n=5) were fabricated and tested. Their mechanical properties were evaluated in 3-point bending using an Instron 1011 tensile testing machine. A machine crosshead speed of 10 mm/min was used. The results indicate that the stiffness and strength of the plates increased significantly as a result of mesh reinforcement. In addition, these properties increased with increasing mesh weight fraction (FIG. 1). The stiffness of the 0.6 wf BFP was significantly higher than the 0.4 and 0.5 wf plates ($p \leq 0.05$). As a result of the new techniques described above, the stiffness of the reinforced BFP was increased by 112% compared to the inventor's initial studies.

In vitro Evaluation:

An *in vitro* study is in progress to the biodegradation characteristics of the BFP. The BFPs are expected to undergo deterioration of their mechanical properties with biodegradation time. Plates with wf of 0.5 and 0.6, which performed best in the dry tests, are currently being subjected to degradation *in vitro* in saline at 37°C. These BFP plates have been affixed to plexiglass plates to simulate *in vivo* conditions where bone will retard the degree of fluid infiltration on one side of the BFP. Eighteen plates of each kind are evaluated. Six plates each of both weight fractions are retrieved and characterized at 3, 6 and 12 weeks. This characterization includes mechanical testing, mass loss and molecular weight. Magnetic resonance imaging is performed at each time period to monitor the degree of fluid infiltration and correlate it with deterioration of the BFPs.

The characterization of specimens subjected to *in vitro* degradation for 3 weeks is shown in Table 2. The results exhibit (Table 2) that the 0.6 wf BFP, although stronger and stiffer as fabricated, undergo a higher rate of degradation of their mechanical properties compared to the 0.5 wf plates.

TABLE 2

Percent reduction at 3 weeks				
wf	Mass	Molecular Weight	Tensile Strength	Elastic Modulus
0.5	10.4	16.7	78.3	66.5
0.6	12.3	10.5	87.8	77.8

The mechanical properties of biodegradable fracture plates are significantly improved. For example, an increase in stiffness of up to 112 percent has been obtained by developing the present fabrication techniques. The effects of varying the amount of mesh reinforcement provides BFPs with improved that are closer to having the mechanical properties necessary to support bone during fracture healing.

The BFP is subjected to *in vitro* degradation in PBS for 6 and 12 week periods and then analyzed for loss in mechanical properties, mass, and molecular weight. As certain BFPs lose their properties rapidly, as is indicated by the 3 week tests, new plates are to be fabricated and coated with a slower degrading polymer to retard fluid infiltration. Magnetic resonance imaging is used to determine the degree of fluid absorption by the plate. Slower degrading polymers, as used in the description of such embodiments of the invention, are well known to those of skill in the art.

* * *

All of the compositions and methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the composition, methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and

modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

The following references, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

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CLAIMS:

1. A biodegradable reinforcement material comprising:

a pharmacologically active substance;

a biodegradable polymer layer; and

a biodegradable reinforcement structure dispersed within the polymer layer;

wherein said biodegradable reinforcement structure comprises a multidirectional arrangement of biodegradable fibers, spears, beads or particles dispersed within the polymer layer, and wherein said reinforcement structure increases the load bearing strength of the material without significantly increasing the stiffness of the polymer layer.

2. The material of claim 1, wherein the fibrous biodegradable reinforcement structure comprises fibers.

3. The material of claim 1, wherein the biodegradable reinforcement structure comprises interwoven threads of PLA, PGA, or a mixture of PLA and PGA.

4. The material of claim 1, wherein biodegradable reinforcement structure comprises a biodegradable mesh.

5. The material of claim 1, wherein said biodegradable reinforcement structure comprises interwoven polymer threads of Vicryl®.

6. The material of claim 5, wherein the interwoven polymer threads comprise about 50% PLA and about 50% PGA.

7. The material of claim 1, wherein the biodegradable reinforcement structure comprises ceramic fibers or beads.

8. The material of claim 1, wherein the biodegradable reinforcement structure comprises polymer beads.

9. The material of claim 1, further comprising a bone growth-inducing factor.

10. The material of claim 1, further comprising an anti-microbial agent.

11. A prosthetic device comprising at least 2 layers of the biodegradable reinforcement material of claim 1.

12. The prosthetic device of claim 11, further defined as comprising a bone growth-inducing factor.

13. The prosthetic device of claim 11, further defined as comprising an anti-microbial agent.

14. The prosthetic device of claim 11, further defined as a biodegradable bone fixation plate.

15. The prosthetic device of claim 11, further defined as comprising between about 10 and about 20 layers of the biodegradable reinforcement material.

16. The prosthetic device of claim 11, wherein the biodegradable reinforcement structure of the material comprises an interwoven mesh of PLA and PGA fibers.

17. The prosthetic device of claim 11, wherein the biodegradable reinforcement structure of the material comprises a biodegradable ceramic mesh.

18. A method of making a biodegradable prosthesis, comprising the steps of:

casting a biodegradable polymer slab;

dispersing a biodegradable reinforcement structure into said polymer to form a reinforced film;

stacking layers of the reinforced film; and

sintering the layers together to form a prosthesis.

19. The method of claim 18, wherein the biodegradable reinforcement structure comprises interwoven PLA fibers.

20. The method of claim 18, wherein the biodegradable reinforcement structure comprises interwoven PGA fibers.

21. The method of claim 18, wherein the biodegradable reinforcement structure comprises interwoven threads of PLA and PGA.

22. The method of claim 21, wherein the biodegradable reinforcement structure comprises a mixture of about 50% PLA and about 50% PGA.

23. The method of claim 18, wherein the sintering step comprises pressuring and heating the film layers in a hydraulic press.

24. The method of claim 18, wherein the biodegradable reinforcement structure is an interwoven series of polymer threads that are dispersed within the polymer slab in a unidirectional orientation, and wherein each reinforced film is stacked into another reinforced film so as to achieve a 90° angle between the orientation of polymer threads in each reinforced layer.

25. The method of claim 18, wherein the prosthesis comprises between about 10 and about 20 stacked layers of the reinforced film.

26. A use of the biodegradable reinforcement material of claim 1 in the preparation of a prosthetic device for use as a bone implant in a mammal.

27. The use of claim 26, wherein said biodegradable reinforcement material further comprises a bone growth-inducing factor.

28. The use of claim 26, wherein said biodegradable reinforcement material further comprises an anti-microbial agent.

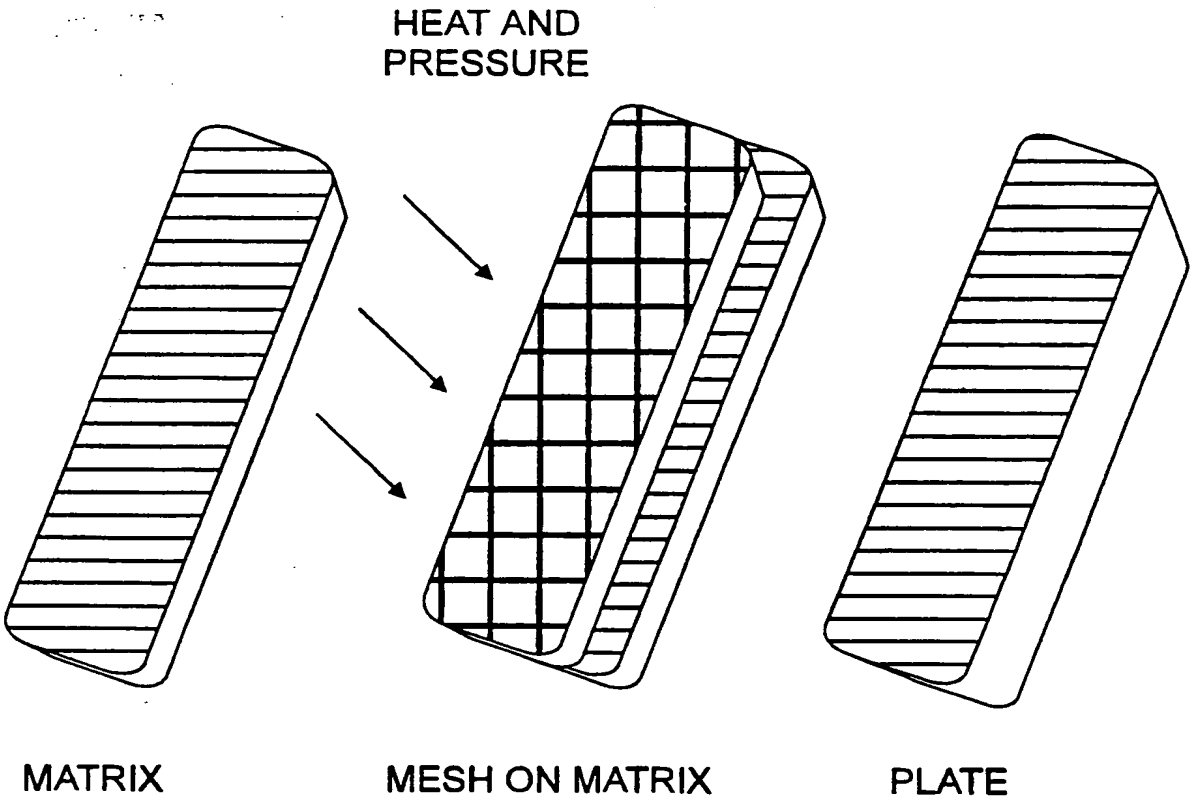

FIG. 1

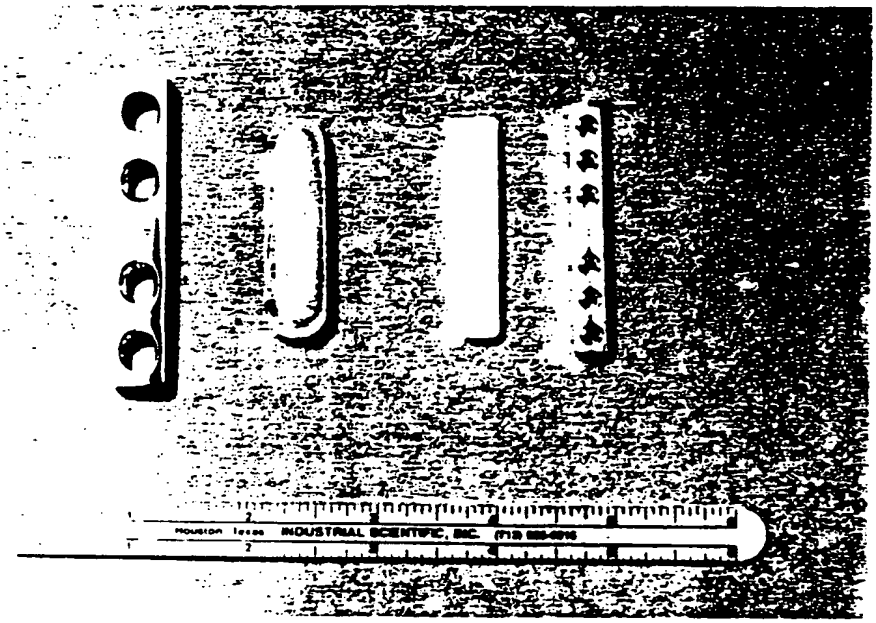

FIG.2

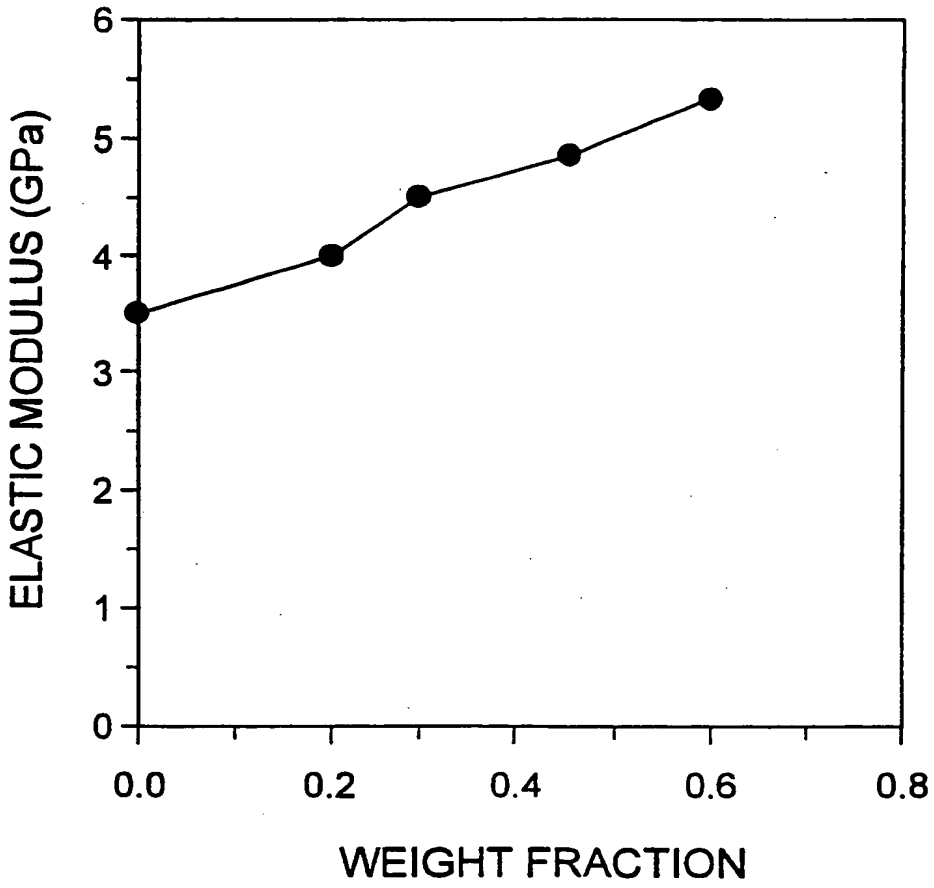

FIG. 3

FIG.4

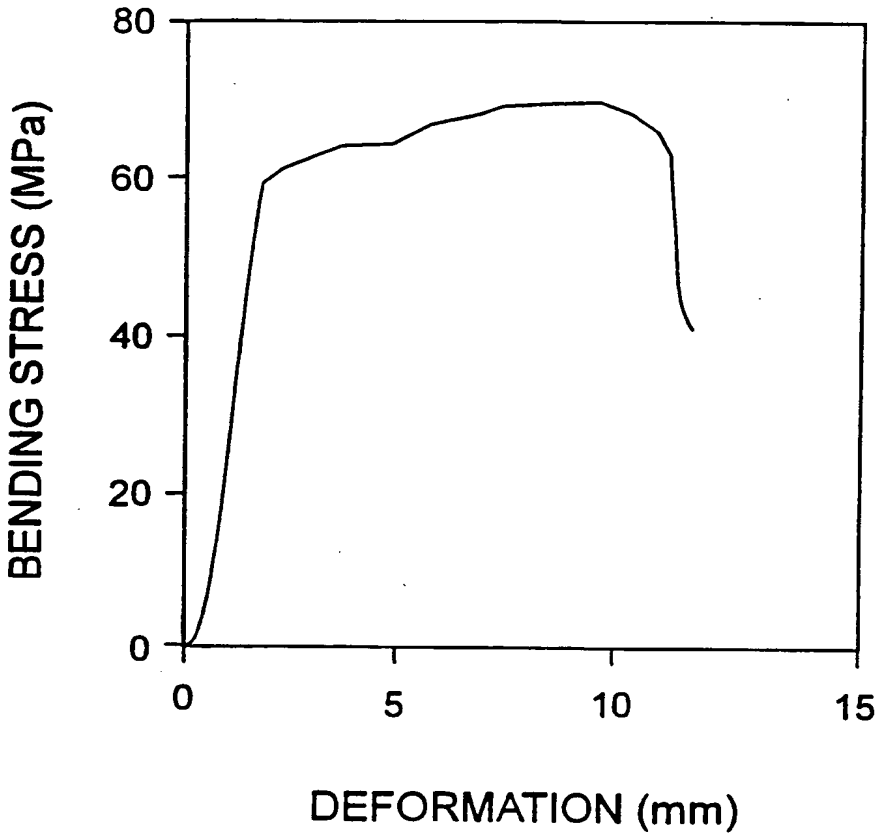

FIG. 5

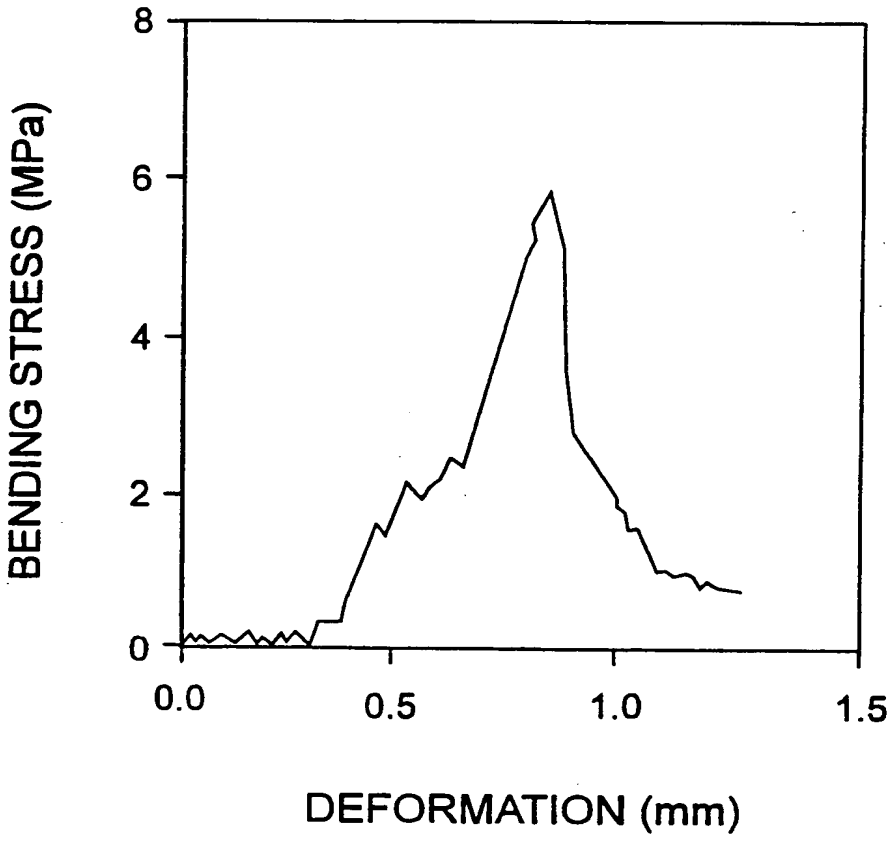

FIG. 6

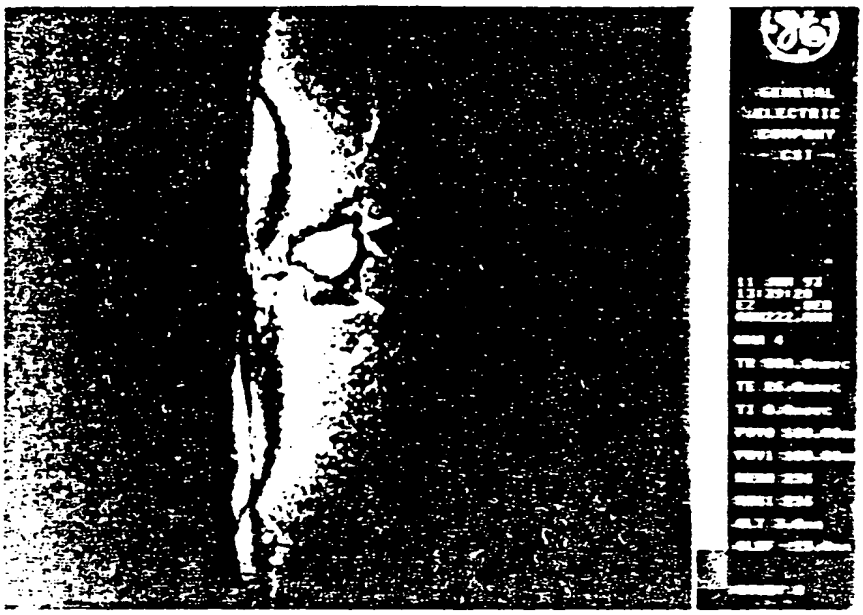

FIG. 7

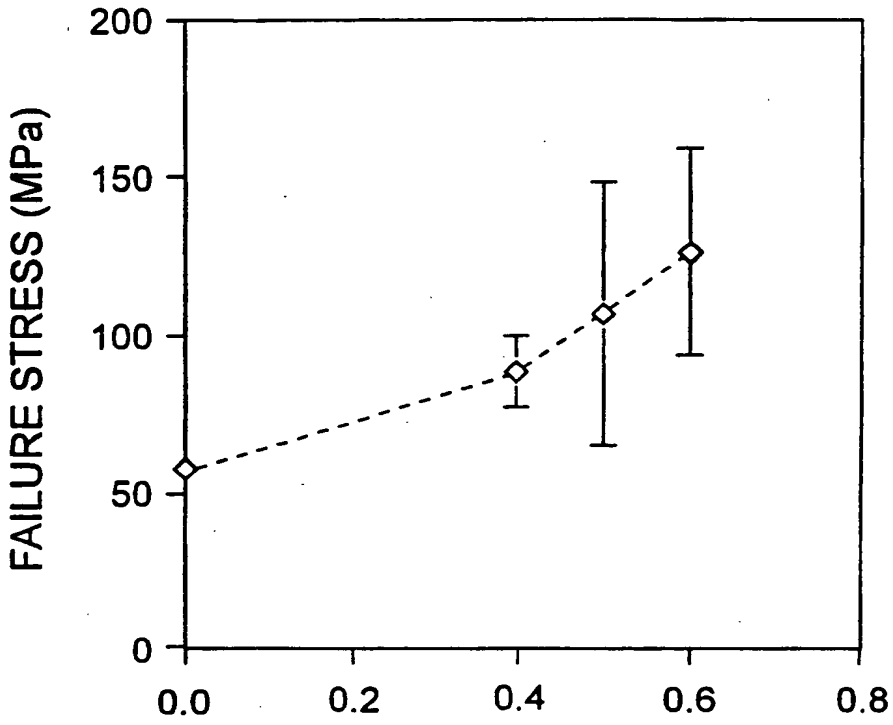

FIG. 8A

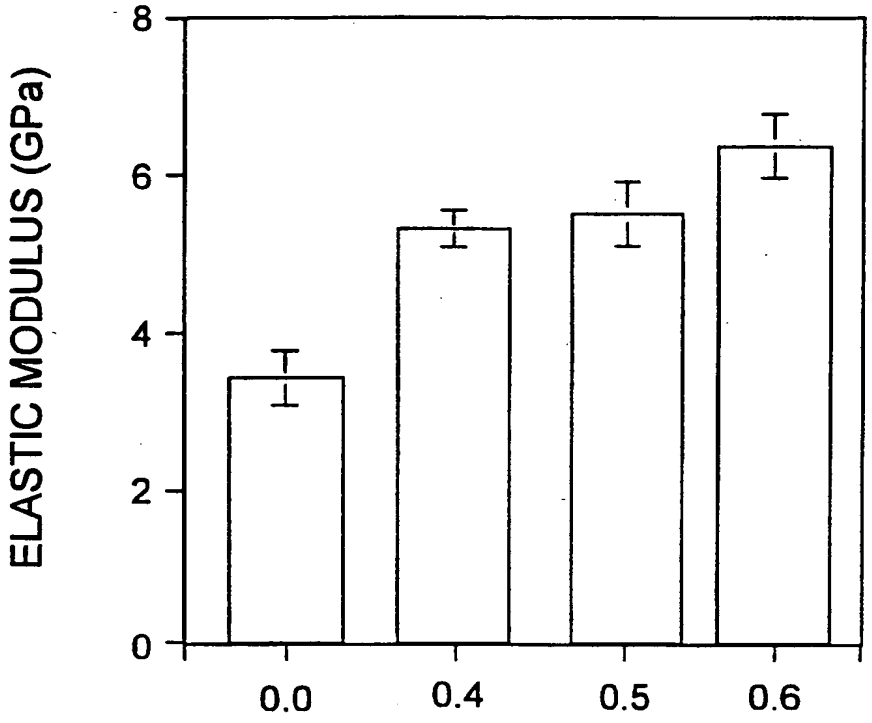

FIG. 8B

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(74) Agents: PARKER, David, L. et al.; Arnold, White & Durkee, P.O. Box 4433, Houston, TX 77210 (US).

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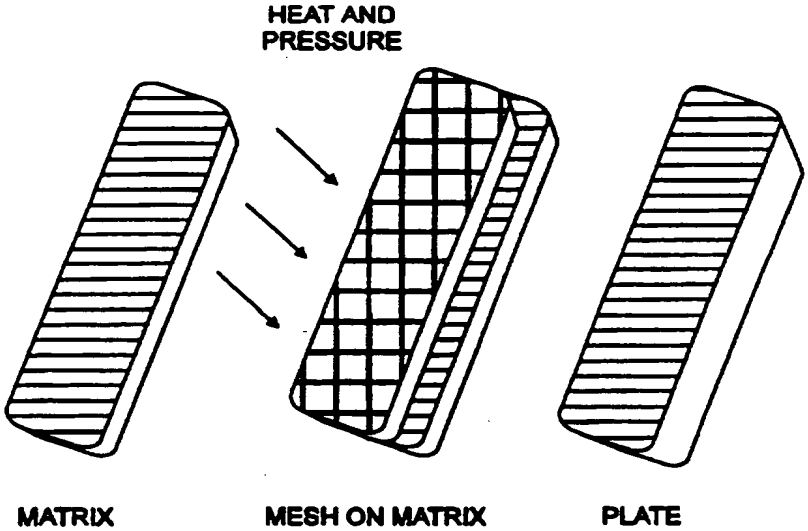
(54) Title: BIODEGRADABLE FRACTURE FIXATION PLATES AND USES THEREOF



(57) Abstract

The present invention provides materials for use in biodegradable structural prosthetic devices with enhanced load-bearing strength and reinforced flexibility. Prosthetic devices are also provided, which comprise a biodegradable polymer layer, reinforced by a biodegradable material, and optionally, the inclusion of pharmacologically active substances, such as growth fact rs and anti-microbial agents. The prosthetic devices provide for gradually decreasing structural support that lessens as the implant degrades and is compensated by new bone growth. The degradati n also provides for the controlled release of the pharmacol gically activ agents. The prosthetic devices are exemplified by bone fixation plates.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 95/08171

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61L31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	EP,A,0 636 377 (JOHNSON & JOHNSON MEDICAL) 1 February 1995 see page 2, line 48 - page 3, line 18; claims; examples ---	1-6, 9-13,27
X Y	US,A,4 279 249 (VERT MICHEL ET AL) 21 July 1981 see column 1, line 38 - column 2, line 39 see column 3, line 53 - column 4, line 7 see claims; examples --- -/--	1-4,14, 18-20 5,7, 9-13,15, 17,25-28

[X] Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
12 December 1995	28. 12. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Cousins-Van Steen, G

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PCT/US 95/08171

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,90 13302 (BRIGHAM & WOMENS HOSPITAL) 15 November 1990	1
Y	see page 10, line 22 - line 31 see page 12, line 1 - line 17 see page 15, line 1 - line 17 see page 24 - page 27 see page 32, line 1 - line 19 see claims	7,9-13, 15,25-28
Y	WO,A,90 04982 (BIOCON OY) 17 May 1990 see page 13, line 15 - line 27 see page 16, line 26 - line 34 see claims 10-12	7,9-13, 17,27,28
Y	EP,A,0 194 192 (ETHNOR) 10 September 1986 see page 7, line 29; claims	5
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1

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Inte- -tional Application No
PC-/US 95/08171

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